The Modulation of Glutathione and Associated Enzymes in Drug Resistance. Kenneth D. Tew, Department of Pharmacology, Fox Chase Cancer Center, 7701 Burholme Avenue, Philadelphia, PA 19111, USA

Glutathione (GSH) is a ubiquitous and abundant tripeptide of glycine, glutamic acid and cysteine. Isolated from representative species of every phylum and reaching intracellular concentrations as high as 5-10 mM, GSH participates in a multiplicity of endogenous synthetic and detoxification reactions. The latter of these functions is critical to tumor cell resistance to those anticancer drugs which produce reactive electrophiles, such as nitrogen mustards, nitrosoureas, platinum drugs and anthracyclines. For the most part, there is only minimal overlap with drugs which are part of the standard MDR phenotype, although it should be noted that a membrane pump specific for the efflux of GSH drug conjugates has been described. A number of key enzymes have been targetted as a means of reversing or modulating tumor cell resistance. For instance, γ-glutamyl cysteine synthetase (γ-GCS) is a rate limiting enzyme in the synthesis of GSH. Thus, intracellular GSH levels, which are frequently elevated in resistant cells, may be depleted by treatment with buthionine sulfoximine (BSO), an inhibitor of γ-GCS (1). Concomitant treatment of BSO with alkylating agents has been shown to enhance cytotoxicity and reverse resistance in preclinical models. Phase I clinical trials with BSO have also been completed (2). Alternative approaches have made use of the fact that glutathione S-transferases (GST) catalyze the conjugation of many anticancer drugs to GSH (3). A complex family of isozymes, GSTs are frequently overexpressed in drug resistant cell lines and in some human cancers (CLL and ovarian cancer). Ethacrynic acid (EA) is both a competitive and non-competitive inhibitor of GST and preclinically is an effective modulator of resistance to alkylating drugs (4). Phase I trials have shown EA to be reasonably tolerated with the diuresis effect as a dose-limiting toxicity (5). More specific and effective inhibitors of GST are under development and may prove to be valuable additions to the available rational approaches to modulating drug resistance.